

AMENDMENTS TO THE SPECIFICATION

Please insert the following section heading and paragraph on page 1, before line 3:

Cross-Reference to Related Applications

The present application is a continuation of International patent application PCT/FR02/02705, filed on July 26, 2002, which claims priority to French patent application 01/10139, filed on July 27, 2001.

Please amend the paragraph beginning on page 11, line 15, as follows:

A preferred peptide of the invention is a fragment of the CD28 protein, and in particular peptides constituted by the sequences PRRPGPTRKHY (SEQ ID No: 33 [[132]]) and (PRRPGPTRK)₂ (SEQ ID No: 34 [[133]]), respectively corresponding to the peptides termed FD2 and FD3 the intracellular penetration capacity and effects on cell viability of which are described below in the experimental section. The present invention also pertains to peptide sequences that are distinguished from the preceding protein by substitution or deletion of amino acids, said distinct sequences nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits.

Please amend the paragraph beginning on page 12, line 1, as follows:

A particularly preferred peptide of the invention is a fragment of the *Vpr* protein of the HIV virus, in particular a fragment of the *Vpr* protein of the HIV-1 or HIV-2 virus, or a sequence that is distinguished from the preceding protein fragment by substitution or deletion of amino acids, said distinct sequence nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits. The invention does not encompass the peptide, a fragment of the *Vpr* protein having the following sequence: LFIHFRIGCQHSRIGITRRRRVRDGSSRP* (SEQ ID NO: 44)

disclosed in the EMBL database, accession number P89821. In contrast, using said peptide in the context of the applications described below falls within the scope of the present invention.

Please amend the paragraph beginning on page 12, line 11, as follows:

Special examples of peptides derived from a protein which interacts with type 2A protein phosphatase derived from protamine that can be cited are the peptide with sequence RRRRRRRSRGRRRRTY (SEQ ID No: 41 [[140]], termed FD8) or a sequence that is distinguished from SEQ ID No: 41 [[140]] by substitution or deletion of amino acids, said distinct sequence nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits.

Please amend the paragraph beginning on page 13, line 1, as follows:

A particularly preferred peptide of the invention is a fragment of the peptide SEQ ID No: 2, said fragment consisting of or comprising the peptide with sequence RHSRIG (SEQ ID No: 36 [[135]]), termed FD9, the capacity for intracellular penetration and the effect on cell viability of which are described below in the experimental section.

Please amend the paragraph beginning on page 13, line 12, as follows:

Particular examples of such polypeptides are the peptide RHSRIG (SEQ ID NO: 36) polymers, and in particular the dimer (RHSRIG)₂ (SEQ ID No: 37 [[136]]) or the trimer (RHSRIG)₃ (SEQ ID No: 38 [[137]]), respectively termed FD10 and FD11, the capacity for intracellular penetration and the effect on cell viability of which are described below in the experimental section.

Please amend the paragraph beginning on page 13, line 23, as follows:

The following sequences can be cited: VEALIRILQQLL (SEQ ID No: 6), ALIRILQQLLFI (SEQ ID No: 7), IRILQQLLFIHF (SEQ ID No: 8), ~~ILQQLLFIHFR~~ ILQQLLFIHFRI (SEQ ID No: 9), RHSRIGIIQRRR (SEQ ID No: 10), SRIGIIQRRRTR (SEQ ID No: 11) and IGIIQRRRTRNG (SEQ ID No: 12) corresponding to dodecapeptides identified as binding the subunit A of PP2A.

Please amend the paragraph beginning on page 14, line 4, as follows:

A particular sequence of the invention that is distinguished from SEQ ID No: 2 by deletion or substitution of amino acids is the sequence RHSRIGVTRQRRARNG (SEQ ID No: 40 [[139]]), also termed FD13 in the experimental section described below.

Please amend the paragraph beginning on page 14, line 18, as follows:

More preferably, a peptide of the invention is characterized in that it is included in one of the following sequences:

- a) RKIGRGKFSEVFEG (SEQ ID No: 3);
- b) ~~TVTKDCVIKILKPVKKKKIKREIKILQNL~~
TVTKDKCVIKILKPVKKKKIKREIKILQNL (SEQ ID No: 4);
- c) KILRLIDWGLAEFYHP (SEQ ID No: 5);
- d) a homologous sequence of SEQ ID No: 3, SEQ ID No: 4 or SEQ ID No: 5 derived from *P falciparum* or *Leishmania*; or
- e) a sequence deriving from the sequences mentioned above by substitution or deletion of amino acids, said distinct sequence nevertheless conserving the properties of binding to protein phosphatase 2A or one of its subunits, and in particular the sequence TVTKDKCVIKILKPVKKKKIKREIKILQNL (SEQ ID No: 43 [[142]]).

Please amend the paragraph beginning on page 15, line 6, as follows:

Among peptides that are distinguished from sequences SEQ ID No: 3, 4 or 5 that can be cited are sequences from site 1 (RKIGRGKFSEVFEG) (SEQ ID No: 3), in particular the peptide with the sequence RKIGRGKFSEVF (SEQ ID NO: 31) and the peptide with sequence IGRGKFSEVFEG (SEQ ID NO: 32) or sequences from site 2 (TVTKDKCIVIKILKPVKKKKIKREIKILQNL) (SEQ ID No: 4), in particular the following peptides:

TVTKDKCIVIKIL (SEQ ID No: 13);

TKDKCIVIKILKP (SEQ ID No: 14);

DKCIVIKILKPVK (SEQ ID No: 15);

CVIKILKPVKKK (SEQ ID No: 16);

IKILKPVKKKKI (SEQ ID No: 17);

ILKPVKKKKIKR (SEQ ID No: 18);

KPVKKKKIKREI (SEQ ID No: 19);

VKKKKIKREIKI (SEQ ID No: 20);

KKKIKREIKILQ (SEQ ID No: 21);

KIKREIKILQNL (SEQ ID No: 22);

and finally sequences from site 3 ~~KILRLIDWGLAEFTHP~~ KILRLIDWGLAEFYHP (SEQ ID No: 5) or the peptide with sequence KILRLIDWGLAE (SEQ ID No: 23), the peptide with sequence LRLIDWGLAEFY (SEQ ID No: 24), or the peptide with sequence LIDWGLAEFYHP (SEQ ID No: 25).

Please amend the paragraph beginning on page 16, line 3, as follows:

One example of a peptide of the invention comprising a sequence homologous to T parva from site 3 of the CK2 α protein in *P falciparum* is the peptide RQKRLI (SEQ ID No: 42 [[141]]).

The invention also encompasses polymers of the peptide RQKRLI (SEQ ID NO: 42) and in particular the trimer (RQKRLI)₃ (SEQ ID No: 35 [[134]]), termed FD7 in the experimental section.

Please amend the paragraph beginning on page 22, line 5, as follows:

Covering the sequence of four peptides 54-57 defines the sequence of site 2

VEALIRILQQLFIHFRI (SEQ ID No: 1)

Peptide 54: VEALIRILQQLL (SEQ ID NO: 6)

Peptide 55: ALIRILQQLLFI (SEQ ID NO: 7)

Peptide 56: IRILQQLLFIHF (SEQ ID NO: 8)

Peptide 57: ILQQLLFIHFRI (SEQ ID NO: 9)

Please amend the paragraph beginning on page 22, line 11, as follows:

Covering the sequence of three peptides 64 to 66 defines the sequence of site 1

RHSRIGIIQRRTRNG (SEQ ID No: 2)

Peptide 64: RHSRIGIIQRR (SEQ ID NO: 10)

Peptide 65: SRIGIIQRRTR (SEQ ID NO: 11)

Peptide 66: IGIIQRRTRNG (SEQ ID NO: 12)

Please amend the paragraph beginning on page 22, line 19, as follows:

Covering the sequence of two peptides defines the sequence of site 1 RKIGRGKFSEVFEG (SEQ ID No: 3)

Peptide 66: RKIGRGKFSEVF (SEQ ID NO: 31)

Peptide 67: IGRGKFSEVFEG (SEQ ID NO: 32)

Please amend the paragraph beginning on page 23, line 1, as follows:

Covering the sequence of ten peptides 74-83 defines the sequence of site 2

TVTKDKCVIKILKPVKKKKIKREIKILQNL (SEQ ID No: 4).

Peptide 74: TVTKDKCVIKIL (SEQ ID NO: 13)

Peptide 75: TKDKCVIKILKP (SEQ ID NO: 14)

Peptide 76: DKCVIKILKPVK (SEQ ID NO: 15)

Peptide 77: CVIKILKPVKKK (SEQ ID NO: 16)

Peptide 78: IKILKPVKKKKI (SEQ ID NO: 17)

Peptide 79: ILKPVKKKKIKR (SEQ ID NO: 18)

Peptide 80: KPVKKKKIKREI (SEQ ID NO: 19)

Peptide 81: VKKKKIKREIKI (SEQ ID NO: 20)

Peptide 82: KKKIKREIKILQ (SEQ ID NO: 21)

Peptide 83: KIKREIKILQNL (SEQ ID NO: 22)

Please amend the paragraph beginning on page 23, line 13, as follows:

Covering the sequence of three peptides defines the sequence of site 3 ~~KILRLIDWGLAEFTHP~~

KILRLIDWGLAEFYHP (SEQ ID No: 5)

Peptide 129: KILRLIDWGLAE (SEQ ID NO: 23)

Peptide 130: LRLIDWGLAEFY (SEQ ID NO: 24)

Peptide 131: LIDWGLAEFYHP (SEQ ID NO: 25)

Please amend Table 1 beginning on page 28, line 1, as follows:

TABLE 1: Peptide sequences containing binding sites for HIV-1 *Vpr* and CK2 α with PP2As

	subunit A	PP2A1
HIV-1 <i>Vpr</i> site 1	RHSRIGIIQQRTRNG (SEQ ID NO: 2)	RHSRIGIIQQRTRNG (SEQ ID NO: 2)
site 2	VEALIRILQQLFIHFRI (SEQ ID NO: 1)	
<i>T. parva</i> CK2 α site 1	RKIGRGKFSEVFEG (SEQ ID NO: 3)	
site 2	TVTKDKCVIKILKPVKKKKIKREIKILQNL (SEQ ID NO: 4)	
site 3	KILRLIDWGLAEFYHP (SEQ ID NO: 5)	KILRLIDWGLAEFYHP (SEQ ID NO: 5)

Please amend the paragraph beginning on page 30, line 1, as follows:

As indicated below, a comparison of the sequences identified by the process of the invention corresponding to the three binding sites with PP2A allows the presence of a motif of the type: **K-I-G/L-R/K**, which is partially repeated in site 2, to be identified.

Site 1: **KIGR** (SEQ ID NO: 45)

Site 2: **KILK**PVKKK**KIKRE****KILQ**NL (SEQ ID NO: 46)

Site 3: **KILR**LI (SEQ ID NO: 47) (partial duplication, KIL/RLI).

Please amend the paragraph beginning on page 30, line 18, as follows:

Site 1

T. parva /*Leishmania* R KIGRGKFSEV FEG (SEQ ID NO: 3)

Pfalciparum/Bovine/Dictyo Y

Please amend the paragraph beginning on page 31, line 1, as follows:

Site 2

T. parva TVTK D K C VIKI LKPVKKKKIKREIKI LQNL (SEQ ID NO: 4)

Pfalciparum ECN R P A V (SEQ ID NO: 48)

Bovine N N- E V E (SEQ ID NO: 49)

Leishmania NN E KV V V E (SEQ ID NO: 50)

Leishmania KVL R Q V -L MV T (SEQ ID NO: 51)

Dictyo

Please amend the paragraph beginning on page 31, line 8, as follows:

Site 3

T.parva K I L RLIDWGLAEFYH P (SEQ ID NO: 5)

Leishmania G K I

Pfalciparum R Q K

Bovine R K

Please amend the paragraph beginning on page 31, line 14, as follows:

A careful analysis of the interactions suggests that the CK2 α from these different species should interact with PP2A; as an example peptide 131 from *T parva* CK2 α described in Figure 2 and in which the first four amino acids of site 3 are deleted is capable of binding PP2A. This suggests that the CK2 α of *Leishmania*, *P falciparum*, which differ in their 3 first amino acids, should bind PP2A. This is consistent with the fact that the KILRLI (SEQ ID NO: 47) motif has a duplicaton of K/R-II/L-I/L which, in a basic context, could be a binding site for PP2A.

Please amend Table 3 beginning on page 31, line 7, as follows:

TABLE 3: Peptides mimicking binding sites for target proteins with PP2As

Original proteins	peptide codes	peptide sequences	SEQ ID No:
CD28			
	FD2	-PRRPGPTRKHY	SEQ ID No: <u>33</u> [[132]]
	FD3	-(PRRPGPTRK)2	SEQ ID No: <u>34</u> [[133]]
CK2 α <i>T parva</i>			
	FD6	-VKKKKIKREIKI	SEQ ID No: 20
CK2 α <i>P. Falciparum</i> (<i>T parva</i> analogue)	FD7	-(RQKRLI)3	SEQ ID No: <u>35</u> [[134]]
<i>Vpr</i> (HIV-1)			
	FD9	-RHSRIG	SEQ ID No: <u>36</u> [[135]]
	FD10	-(RHSRIG)2	SEQ ID No: <u>37</u> [[136]]
	FD11	-(RHSRIG)3	SEQ ID No: <u>38</u> [[137]]
	FD12*	-(AHSRIG)(AHSRIG)3 (FD11 mutation, R...A)	SEQ ID No: <u>39</u> [[138]]
	FD13	RHSRIGVTRQRRARNG (FD14 analogue)	SEQ ID No: <u>40</u> [[139]]
	FD14	RHSRIGIIQQRTRNG	SEQ ID No: 2
Protamine	FD8	RRRRRRRRSRGRRRRRTY RRRRRRRRSRGRRRRRTY	SEQ ID No: <u>41</u> [[140]]

Please replace the previously submitted Sequence Listing filed with the Preliminary Amendment on September 26, 2005, with the attached substitute Sequence Listing beginning on new page 43.